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WONG, K	
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DATE MAILED: 05/09/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-37 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☒ Claims 35 are allowed.
4. ☒ Claims 1-34, 36, 37 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☒ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☒ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-93)

1. Claims 1, 33, 36 and 37 are generic to a plurality of distinct species comprising nonheterocyclic or heterocyclic groups as R_1 and H or protected carboxy groups as R_2. These inventions are classified differently. Election of a disclosed single species is required under 35 U.S.C. 121. During a telephone conversation with Mr. Thomas Rizzo on 04/28/97, applicants elected with traverse the compound of Example 111 as the species. The full scope of claims 1-37 is examined on the merits for this office action.

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 1, 33, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Afonso et al (Ref. A, US 4,540,579), which teaches (5R,6R,8S)-6-(1-hydroxyethyl)-2-(amino acid alkyl)penem-3-carboxylic acids useful as antibacterial agents and the hydroxy-protected derivatives thereof useful as intermediates for making said antibacterial agents (e.g. see column 2, lines 19-27; column 1, lines 32-40; columns 3 and 4, Scheme I, compounds (IX) and (I); column 18, claim 1). Afonso et al differs from claims 1, 33, 36 and 37 in teaching a 1-hydroxyethyl, instead of a 1-hydroxypropyl, group at the 6-position of the penems. However, the compounds of Afonso et al are adjacent homologs of the instant compounds. Adjacent homologs

have close structural similarity and it is known in the art that compounds of close structural similarity have similar properties. It would have been obvious to one of ordinary skill in the art to create the compounds of claims 1, 36 and 37 because the artisan would have been motivated to modify the 1-hydroxyethyl derivatives taught by Afonso et al. by making the adjacent homolog, i.e. the 1-hydroxypropyl derivatives, in order to obtain additional penems useful as antibacterial agents.

Since Afonso et al also teaches the hydroxy-protected version of its penems useful as intermediates for making said penems (e.g. see the analogous process in columns 3 and 4, Scheme I, Ref. A), the hydroxy-protected compounds of claim 33 would have been obvious because the artisan would have been motivated to modify the hydroxy-protected 1-hydroxyethyl derivatives of Afonso et al by making the adjacent homologs, i.e. the hydroxy-protected 1-hydroxypropyl derivatives, in order to obtain additional intermediates for making antibacterial penems.

4. Claims 1, 17-19, 32-34, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Girijavallabhan et al (Ref. R, *Tetrahedron Lett.*, vol. 22, pp. 3485-3488, 1981), which teaches a 5R,6R,1'S isomer of a penem useful as an antibacterial agent (e.g. see p. 3487, Scheme 3, Compound (23)). That penem of Ref. R differs from the compounds of claims 1, 17-19, 32-34, 36 and 37 in having a 1-hydroxyethyl, instead of a 1-hydroxypropyl, group at the 6-position of the penems. However, the compound of Ref. R is an adjacent homolog of the instant

compounds. Adjacent homologs have close structural similarity and it is known in the art that compounds of close structural similarity have similar properties. It would have been obvious to one of ordinary skill in the art to create the compounds of claims 1, 17-19, 32, 36 and 37 because the artisan would have been motivated to modify the 1-hydroxyethyl derivative of Ref. R by making the adjacent homolog, i.e. the 1-hydroxypropyl derivative, in order to obtain an additional penem useful as antibacterial agent.

Since Ref. R also teaches the hydroxy-protected version of its penem useful as an intermediates for making said penem (e.g. see p. 3487, first paragraph, the second and fourth sentences), the hydroxy-protected compounds of claims 33 and 34 would have been obvious because the artisan would have been motivated to modify the hydroxy-protected 1-hydroxyethyl derivative of Ref. R by making the adjacent homolog, i.e. the hydroxy-protected 1-hydroxypropyl derivative, in order to obtain an additional intermediate for making antibacterial penems.

5. Claims 1-34, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ishiguro et al (Ref. L, JP 04069387 A2; see Ref. T, *Derwent Abstract*, No. C92-059274 and Ref. U, *Chemical Abstract*, No. 117:90047 for the English abstracts), which teaches 5R,6R-cis-penem derivatives substituted, at the 6-position, by hydroxyalkyl, in which the hydroxy may be protected, useful as antimicrobial agents (e.g. see formula (Ia) in pages 1 and 3, Ref. L; also see formula (Ia) and the abstract, Ref. T; also see compounds of Registry No. 132950-27-7, 132970-59-3, 133006-89-0 and 133885-57-1, Ref. U, for the closest prior art compounds). The penems

prepared by Ishiguro et al (see compounds of Registry No. 132950-27-7, 132970-59-3, 133006-89-0 and 133885-57-1, Ref. U) differ from the instant penems in having a 1-hydroxyethyl, instead of a 1-hydroxypropyl, group at the 6-position. However, Ishiguro et al teaches that hydroxy-(C_1-C_4)alkyl groups will all work at the 6-position (e.g. see p. 3, right column, Ref. L). It would have been obvious to one of ordinary skill in the art to make the penems of claims 1-32, 36 and 37 because the artisan would have been motivated to modify the 1-hydroxyethyl 1'S,5R,6R-cis-penem examples of Ishiguro et al (Ref. L) by replacing the 1-hydroxyethyl group with an 1-hydroxypropyl group, in the compounds of Registry No. 132950-27-7, 132970-59-3, 133006-89-0 and 133885-57-1, Ref. U, supplemented with optional replacement of the methoxymethyl or tetrahydrofuranyl radical at the 2-position of these compounds with other $-(CH_2)_nR^4$ or $-SR^4$ radicals with R^4 representing optionally substituted alkyl, aryl, aralkyl or heterocyclyl groups mentioned in p. 3, the left and right columns, Ref. L (e.g. tetrahydrofuran, tetrahydropyran, 1,3-dioxolane, 1,4-dioxalane, pyrrolidine, quinoline, isoquinoline, thiophene, pyrrole, furan, tetrazole, imidazole, thiazole or triazole) or replacement of the free carboxy group at the 3-position with esters, in order to obtain additional 5R,6R-cis-penem derivatives useful as antimicrobial agents. Since Ishiguro et al teaches protecting the hydroxy radical in the hydroxyalkyl group at the 6-position (e.g. see p. 3, right column), the compounds of claims 33 and 34 would also have been obvious because the artisan would have been motivated to protect the 1-hydroxypropyl group in order to obtain additional useful 5R,6R-cis-penem derivatives.

6. Claims 1-4, 7-19, 31-34, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sunagawa et al (Ref. B, US 4,742,052), which teaches that (1'S,5R,6R)-6-(1-hydroxyethyl)penem compounds, wherein the hydroxy group of the 1-hydroxyethyl group at the 6-position may be protected and the carboxy group at the 3-position may also be protected, are useful as antibacterial agents (note that 1'S,5R,6R is the same as 5R,6R,8S; e.g. see column 1, line 23 to column 2, line 68; column 3, line 1 to column 5, line 17; column 6, line 58 to column 7, line 30; column 7, lines 42-61 wherein the 1'S,5R,6R isomer is preferred; for the closest prior art compounds, see column 18, Example 1, column 20, Example 2, column 22, Example 3, column 23, Example 4, column 37, Example 33, column 43, Example 43, column 43, Example 45 and column 47, Example 50). The penems of Sunagawa et al differ from the penems of claims 1-37 in having 1-hydroxyethyl, instead of 1-hydroxypropyl, at the 6-position. However, they are adjacent homologs with close structural similarity. Since compounds of close structural similarity would have been expected to have similar properties, the penems of claims 1-4, 7-19, 31-34, 36 and 37 would have been obvious to one of ordinary skill in the art because the artisan would have been motivated to modify the compounds of Sunagawa et al by making the 1-hydroxypropyl derivatives in order to obtain additional antibacterial agents using the above closest prior art compounds as guidance supplemented by three other teachings of Sunagawa et al: (1) the hydroxy group may be protected by conventional hydroxy-protecting groups (e.g. see column 1, line 18-20; column 2, lines 53-68, Ref. B), (2) other radicals would work for R_2 (e.g. see column 1, line 23 to column 2, line 50; column 3, line 1 to column 4, line 68; as well as the

R_2 radicals illustrated by other examples prepared by Sunagawa et al) and (3) H atom, carboxy-protecting groups or salt-forming groups would work for R_3 (e.g. see column 2, lines 51-52 and column 5, lines 4-24).

7. Claims 1, 30, 31, 33, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menard et al (Ref. C, US 4,272,437), which teaches that 6-(1-hydroxyalkyl)-penems are useful as antibacterial agents (e.g. column 3, line 63 to column 12, line 25, Ref. C). At the 6-position of the penems, Menard et al teaches that lower alkyl substituted by OH at the alpha-carbon atom is preferred (e.g. see column 13, lines 56-59, Ref. C). Since 1-hydroxypropyl is exemplified in column 257, Example 67, Menard et al does suggest 1-hydroxypropyl as Y at the 6-position (Ref. C). Also Menard et al teaches that the hydroxy group at the 6-position substituent and the carboxy group at the 3-position may be protected (e.g. see column 16, lines 37-39; columns 257 and 263, Example 67; column 17, lines 20 and 35; column 18, line 20; and column 19, lines 4-5, Ref. C). Since the penems of Menard et al can have asymmetric carbon atoms, Menard et al teaches that the penems can exist in four isomeric forms and its invention includes the individual resolved isomers (e.g. see column 12, lines 34-55). Menard et al calls a mixture of 1'S,5R,6R and 1'R,5S,6S penems as "isomer A" (e.g. see column 245, line 11, Example 61). The compounds of Menard et al in the isomer A form differ from the instant compounds in being a mixture of 1'S,5R,6R and 1'R,5S,6S, instead of only 1'S,5R,6R. However, among all the geometric isomeric forms of the penems, Menard et al prefers those with a 5R

configuration, i.e. the configuration of natural penicillins, at the 5-position (e.g. see column 12, lines 39-42). Since in the mixture of 1'S,5R,6R and 1'R,5S,6S penems in isomer A, only the 1'S,5R,6R penems have a 5R configuration at the 5-position, one of ordinary skill in the art reading the disclosure of Menard et al on its "isomer A" form would be led to prefer the 1'S,5R,6R penem over the 1'R,5S,6S penem in the mixture. Therefore, the penems of claims 1, 30, 31, 36 and 37 would have been obvious because the artisan would have been motivated, in order to obtain additional penems useful as antibacterial agents, to modify the penem of Example 61 of Menard et al in two ways: (1) by replacing the 1-hydroxyethyl group at the 6-position with an 1-hydroxypropyl group as exemplified by Example 67, supplemented by optional replacement of the methyl group at the 2-position with other radicals as generically taught by Menard et al in column 4, lines 60-65, as exemplified in other examples prepared by Menard et al (e.g. see columns 38, 46, 47, 53, 59, 70, 76, 83, 84, 93, 103, 105, 125, 126, 127, 129, and 134, Example 19, Example 20, Example 22, Example 27, Example 29, Example 31, Example 38, Example 41, and Example 76) and (2) by isolating the 1'S,5R,6R form. Additionally, Menard et al teaches that the hydroxy radical at the 1-hydroxyalkyl group at the 6-position may be protected with conventional blocking groups to make intermediates for the preparation of antibacterial penems (e.g. see column 16, lines 37-41; column 27, lines 13-22; and Example 67, columns 257 and 263). So the compounds of claim 33 would have been obvious because the artisan would have been motivated to protect the hydroxy group at the 1-hydroxypropyl radical at the 6-position in order to obtain intermediates for making the above additional antibacterial penems.

8. Claims 1-34, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gosteli et al (Ref. D, US 4,692,442), which teaches that penems substituted with 1-hydroxyethyl at the 6-position are useful as antibacterial agents (e.g. see claims 1 and 4, columns 75 and 76). The penems of claims 1 and 4 of Gosteli et al differ from the instant penems in having a 1-hydroxyethyl, instead of 1-hydroxypropyl, at the 6-position. However, Gosteli et al teaches that methyl, ethyl, 1-hydroxyethyl, 1-hydroxyethyl or 2-hydroxyprop-2-yl would all work at the 6-position (e.g. see column 20, lines 20-21). Gosteli et al also teaches that the free carboxy group at the 3-position could be replaced by esters or protected carboxyl groups (e.g. see column 2, lines 28-30). For the substituent at the 2-position, Gosteli et al teaches that alkylthio, alkenylthio, cycloalkylthio, phenylthio or heterocyclylthio work work (e.g. see column 11, line 22, to column 12, line 11). Therefore, it would have been obvious to make the penems of claims 1-32, 36 and 37 because the artisan would have been motivated to modify the penems of claims 1 and 4 of Gosteli et al using Examples 5 (column 45), 63 (column 66), 64 (column 67), 68 and 69 (column 69) and 88 (columns 74 and 75) as guidance by replacing the 1-hydroxyethyl with 1-hydroxypropyl, supplemented by Gosteli's teachings that the 3-carboxy group may be protected or the alkylthio or alkenylthio group at the 2-position may be replaced with cycloalkylthio, phenylthio or heterocyclylthio in order to obtain additional penems useful as antibacterial agents. Since Gosteli et al also teaches that the hydroxy radical in the hydroxyalkyl group may be protected (e.g. see column 3, lines 12-17), the penems of claims 33 and 34 would also have been

obvious because the artisan would have been motivated to protect the hydroxy radical in the 1-hydroxypropyl group in order to obtain additional antibacterial agents.

9. Claims 1-32, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leanza et al (Ref. E, US 4,748,162), which teaches that penems are useful as antibacterial agents (e.g. see claim 7 in columns 58-64 and claim 12 in columns 64-68). The penems of claims 7 and 12 of Leanza et al differ from the instant penems in not limiting to only 1-hydroxypropyl at the 6-position. However, 1-hydroxypropyl at the 6-position is preferred by Leanza et al (e.g. see column 18, line 26) and is shown in Compounds 83-89 in column 45. Therefore it would have been obvious to make the penems of claims 1-32, 36 and 37 because the artisan would have been motivated to modify Compounds 83-89 of Leanza et al using the generic teachings of claims 7 and 12 on different -SR^8 radicals that would work in order to obtain additional penem derivatives useful as antibacterial agents.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1, 36 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Minamida et al (Ref. M, EP 0 069 373), which teaches a 6-(1-hydroxypropyl)-penem meeting the limitations of claims 1, 36 and 37, wherein R^1 is 1-methyltetrazol-5-ylthio (e.g. see the last compound in p. 11).

12. Claims 1, 33, 36 and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Minamida et al (Ref. M, EP 0 069 373), which teaches that (5R,6R)-1-hydroxyalkyl penems are useful as antibacterial agents (e.g. see formula (I), p. 1, line 5 to p. 7, line 10) and, more specifically, (1'S,5R,6R)-1-hydroxyalkyl penems (e.g. see p. 17, line 27). Minamida et al differs from claims 1, 36 and 37 in generically teaching 1-hydroxyalkyl, instead of 1-hydroxypropyl, at the 6-position. However, Minamida et al does exemplify 1-hydroxypropyl at the 6-position in p. 11. Therefore, it would have been obvious to make the penems of claims 1, 33, 36 and 37 because the artisan would have been motivated to modify the last compound in p. 11 using the substituents in Examples 4 (p. 68), 6 (p. 69), 7 (p. 70), 8 (p. 71) and 12 (p. 74) as guidance, optionally supplemented by the teachings in p. 1, lines 11, 12 and 16 and p. 6, lines 6-21, on the different R^3 and R^6 groups that would work or the teachings in p. 6, line 38 to p. 14, on the different R^4 and R^5 groups that would work in order to obtain additional antibacterial agents.

13. Claim 35 is deemed allowable because the art does not teach or suggest penems with 1-hydroxypropy at the 6-position and sulfydryl at the 2-position.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to K.L. Wong via telephone at (703) 308-4723 or facsimile at (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

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SUPERVISORY PATENT EXAMINER
GROUP 1200

K.L.W.
May 7, 1997